(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 April 2004 (15.04.2004)

PCT

(10) International Publication Number
WO 2004/031731 A3

(51) International Patent Classification[7]: A61K 38/00, C07K 7/00

(21) International Application Number: PCT/US2003/031321

(22) International Filing Date: 1 October 2003 (01.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/415,867 2 October 2002 (02.10.2002) US
60/442,005 22 January 2003 (22.01.2003) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 3 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR CONTROLLING PROLIFERATION OF CELLS

(57) Abstract: An isolated nucleostemin polypeptide is disclosed herein. The nucleostemin polypeptide includes an amino acid sequence at least 85% identical to SEQ ID NO:2. In several examples, the polypeptide regulates cell differentiation, cell proliferation, or both. Nucleic acids encoding these polypeptides, vectors including the nucleic acids, and host cells transfected with these nucleic acids are also disclosed. Methods for inducing differentiation, inhibiting proliferation, and inducing senescence of a cell by altering the level of a nucleostemin polypeptide including an amino acid sequence at least 80% identical to SEQ ID NO: 2 are also disclosed. Methods for screening for agents that affect proliferation, differentiation. Or senescence of cells are also disclosed.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/31321

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00; C07K 7/00
US CL : 530/324; 514/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/324; 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2003/0008284 A1 (KENNEDY et al) 09 January 2003 (01.09.03), see [0215] and [0204]	1-2, 11-14 ---------- 23-26,30-32
X	Database Genseq, Alexandria, VA, AN AAM48961, KENNEDY et al, 'Detecting a cancerous colon cell, useful for diagnosing colon cancer and for rational drug and therapy design, comprises detecting at least one differentially expressed gene product' WO 01/196523 20 December 2001 (20.12.01).	1-2,11-14
X	Database Genseq. Alexandria, VA. AN AAB43305, SHIMKETS et al 'Novel nucleic acids and petpides derived from open reading frame X, useful for treating e. g. cancers, proliferative disorders, neurodegenerative disorders and cardiovascular disease', WO 00/05873 05 October 2000 (05.10.00).	1-2,11-14
X	Database Genseq, Alexandria, VA, AN AAB86210, 'new nucleic acid encoding interactors of Fanconi anemia protein, useful for diagnosis, treatment and prevention of e. g. DNA-repair defects or cell-cycle disorders', WO 01/140461 07 June 2001 (06.07.01).	1-2,11-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
29 December 2004 (29.12.2004)

Date of mailing of the international search report
25 JAN 2005

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/31321

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: claims 1-14 (SEQ ID NO. 2 and 6) and claims 23-36, 40-54 (SEQ ID NO. 6)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/31321

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-14, drawn to nucleostemin polypeptide.

Group II, claim(s) 15-22, drawn to isolated polynucleotides. Vectors and host cells.

Group III, claim(s) 23-36, 40-54 drawn to method for inducing differentiation or inhibiting proliferation of a cells by altering the level of nucleostemin.

Group IV, claim(s) 37-39, drawn to method of screening for agents that affect differentiation or proliferation of a cell.

Group V, claim(s) 55-62, drawn to method for inducing differentiation, inducing senescence or inhibitng proliferation of a cell.

Group VI, claim(s) 63, drawn to antibody directed against the polypeptide of claim 1.

In addition, with Group I, applicant will have SEQ ID NO. 2 examined without paying additional fees.
In addition, if applicant pays for Group II, they will get Group II as it reads on SEQ ID NO. 1. If applicant wants any more sequences, they need to pay additional fees.
In addition, if applicant pays for Group III, they will get Group III as it reads on SEQ ID NO. 6. If applicant wants any more sequences, they need to pay additional fees.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Each of the products of Group I-II and VI differ structurally and functionally and this lack the same or corresponding special technical feature. Each of the methods of Group III-V require the use of different products. The product required in Group III is a polypeptide. The product in Group IV is any agent. The product in Group V is a polypeptide different from that in Group III.

According to PCT Rule 13.2 and to the guidelines in Section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions, all alternatives of a Markush Group must have a common structure, which is a significant structural element. Although SEQ ID No. 1 and 3 share a common structure of a single nucleic acid, the compounds are not regarded as being of similar nature because the shared common structure is not a significant structural element. A common structure of a single nucleic acid is not a significant structural element because the nucleic acid is found in every nucleic acid sequence.

According to PCT Rule 13.2 and to the guidelines in Section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions, all alternatives of a Markush Group must have a common structure, which is a significant structural element. Although SEQ ID No. 2 and 4 and 6 and 8 and 10 share a common structure of a single amino acid, the compounds are not regarded as being of similar nature because the shared common structure is not a significant structural element. A common structure of a single amino acid is not a significant structural element because the amino acid is found in every amino acid sequence.